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SYNTHESIS OF ANTIMALARIAL AGENTS FROM 2,3-DIHYDRO-1,6-DIAZAPHEN--ETC(U)
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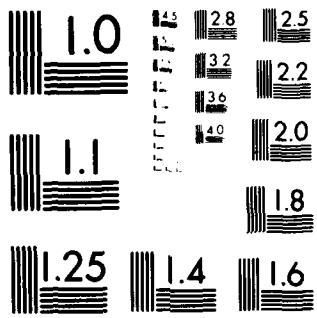

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REPORT NUMBER FOUR

SYNTHESIS OF ANTIMALARIAL AGENTS FROM 2,3-DIHYDRO-1,6-DIAZAPHENALENE DERIVATIVES

Annual Summary Report

January, 1979 to December, 1979

JAMES M. COOK

December, 1979

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

Contract No. DAMD17-78-C-8003

Department of Chemistry
University of Wisconsin-Milwaukee
Milwaukee, Wisconsin 53201

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19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

1,6-diazaphenalene, 5,8-diaminoquinoline analogs
9-methoxy-1,6-diazaphenalene, 7-nitro-2,5-dichloro-1,6-diazaphenalene
malaria, leishmaniases

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The nitration of 1,6-diazaphenalene 1 has been difficult for the major product resulted from nitration of both positions -3 and -7 of 1, however, the problem of mononitration has been solved by the use of a $NaNO_2/CF_3CO_2H$ nitration mixture at -63°C. This procedure gave the desired mononitro compound 17 in 40% yield and some unreacted starting material. Because of the earlier difficulty with mononitration of 1,6-diazaphenalene, a new procedure was required to functionalize the 9-methoxy-1,6-diazaphenalene analogs. This set-back has been

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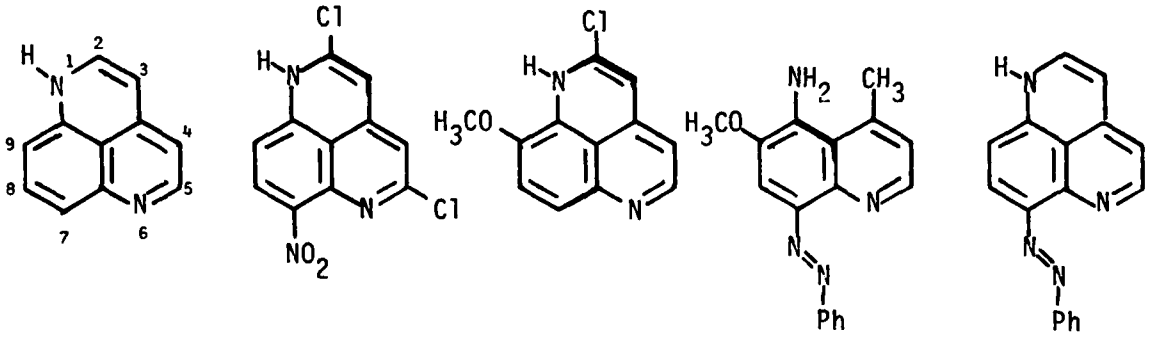
overcome by stirring either 4-methyl-5-amino-6-methoxyquinoline or 1,6-diazaphenalene 1 with phenyldiazonium chloride to provide the 5,8-diamino-compound 25 or the 7-functionalized diazaphenalene 19, respectively. It is planned to use this technology to incorporate an amine function into position -7 of 2-chloro-9-methoxy-1,6-diazaphenalene 2 and to convert 2, 17, 19 and 25 to the target compounds during the next year.



1 17 2 25 19

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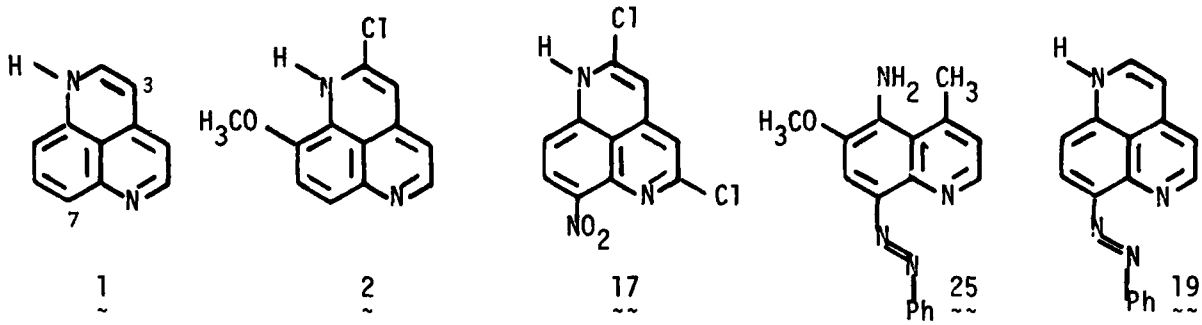
SUMMARY

In agreement with our original synthetic plan methyl-5,6,7,8-tetrahydro-5-oxocoumarin-4-yl acetate was converted to 1,6-diazaphenalene 1; moreover a



1 2 17 25 19

cursory examination of the mechanism of the "modified Semmler Wolff" step has now permitted the use of phenylphosphonic dichloride in place of the trifluoroacetic acid/trifluoroacetic anhydride mixture in this reaction. This effects both aromatization and chlorination of the precursor to 1 in a single step. The synthesis of 1 can now be accomplished in six simple steps from cyclohexane-1,3-dione, furthermore, three of these steps are of a trivial nature (see Scheme I).

A major obstacle in the program has centered on the incorporation of nitrogen at position-7 of 1 instead of substitution at position-3. After a long and laborious study it was discovered that 2,5-dichlorodiazaphenalene can be converted to the desired 7-nitro-2,5-dichloro-1,6-diazaphenalene 17 in 40-60% yield by stirring the dichloro derivative in a mixture of trifluoroacetic acid/sodium nitrite at -63°C. Preliminary experiments indicate that the nitro and chloro groups of 17 can be reduced in a single step to provide a 7-aminodiazaphenalene, however, complete characterization of the product must still be carried out.

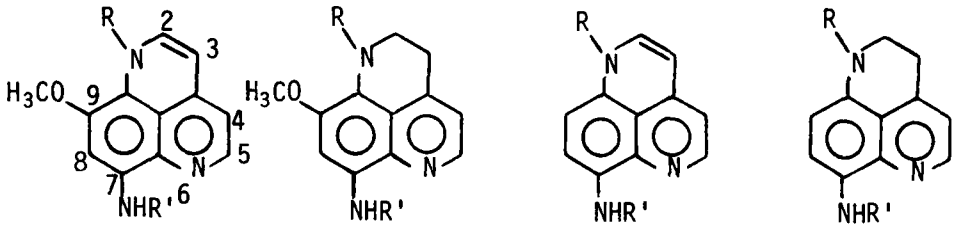
In an effort to find a more selective means of electrophilic substitution at position-7, phenyldiazonium chloride (weak electrophile) has been stirred with 1 and in a parallel experiment with 4-methyl-5-amino-6-methoxy quinoline. The results are quite exciting for in both cases only the products of mono-substitution were observed which provided 19 and 25, respectively. The studies with phenyldiazonium chloride and trifluoroacetic acid/sodium nitrite clearly indicate that an amine function can be incorporated into position-7 of 1,6-diazaphenalene 1 or into the analogous position of 2-chloro-9-methoxy-1,6-diazaphenalene 2.

Since the preparation of 1, 2, 17, 19, and 25 have been accomplished all that remains is to convert these compounds to the desired 7-amino derivatives followed by alkylation to provide the desired target compounds.

Finally, the properties of 1,6-diazaphenalene 1 have been investigated vis a vis its potential as a drug. It has been found that the pK_a of 1 is 6.56 and resembles quite closely the pK_a of imidazole. This supports our previous contention that 1 is a vinylogous imidazole. Despite this, solubility studies have demonstrated that the lipophilicity of 1,6-diazaphenalene 1 was much closer to quinoline than to that of imidazole, which is important, we feel, in terms of drug potential in the antimalarial area.

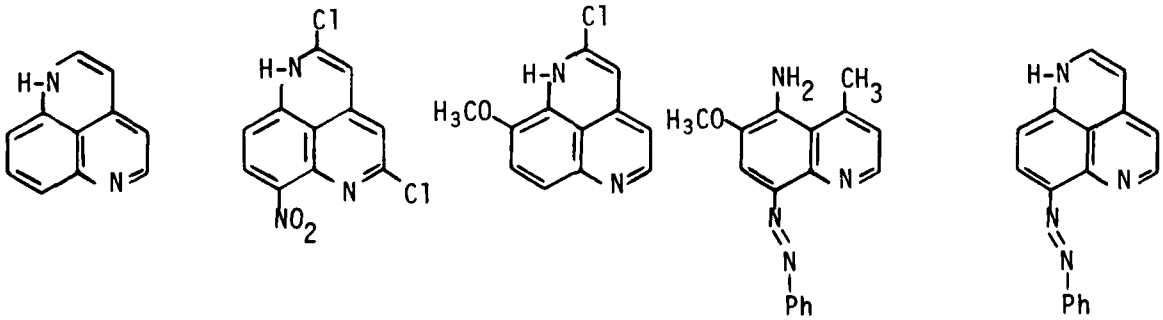
FOREWARD

The following report concerns research directed toward the synthesis of potential antimalarial agents, based on the structures of 9-methoxy and 9-H-7-alkylamino-1,6-diazaphenalene bases (A, C) and their 2,3-dihydro analogs (B, D); the resemblance to 5,8-diaminoquinolines, however, is not accidental.



A B C D

The nitration of 1,6-diazaphenalene 1 has been difficult for the major product resulted from nitration of both positions-3 and -7 of 1, however, the problem of mononitration has been solved by the use of $NaNO_2/CF_3CO_2H$ nitration mixture at -23°C to -63°C. This procedure gave the desired mononitro compound 17 in 40%yield and some unreacted starting material. Because of the earlier difficulty with mononitration of 1,6-diazaphenalene, a new procedure was required to functionalize the 9-methoxy-1,6-diazaphenalene analogs. This set-back has been overcome by use of phenyldiazonium chloride to provide 19 and 25. It is planned to use this technology to incorporate an amine function into position -7 of 2-chloro-9-methoxy-1,6-diazaphenalene 2 and to convert 2, 17, 19 and 25 to the target compounds during the next year.



1 17 2 25 19

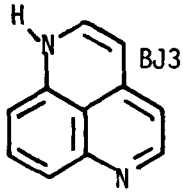
This report is not written in chronological order, in an historical sense, but the most interesting results are presented first. The synthesis of 1,6-diazaphenalene 1 is presented followed by an improved (5-step) synthesis of the molecule based on mechanistic considerations. A study of the chemistry of 1 with regard to electrophiles is discussed which led to the preparation of the important amine, 7-amino-1,6-diazaphenalene 15, while the construction of 6-methoxy-1,6-diazaphenalene is also described. The physical properties of 1,6-diazaphenalene are described with regard to its drug potential (vinylogous imidazole) while the last portion of the report is the experimental section.

TABLE OF CONTENTS

FRONT COVER	i
ABSTRACT (DD Form 1473)	ii
TITLE PAGE	iv
SUMMARY	v
FOREWARD	vi
TABLE OF CONTENTS	1
INTERMEDIATES SUBMITTED FOR SCREENING	2
WORK IN PROGRESS	2
EXPERIMENTAL	14
REFERENCES	23
DISTRIBUTION LIST	24

A.

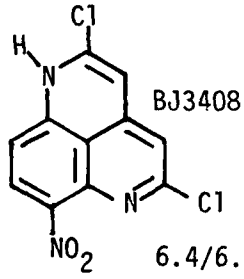
1. Intermediates sent for screening whose structures have been unambiguoulsy assigned.



BJ34090

6.0/6.1

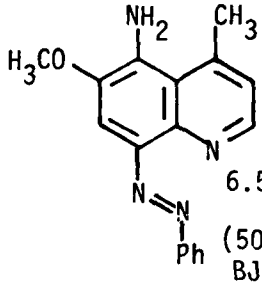
(500 mg)
BJ34090



BJ34081

6.4/6.1

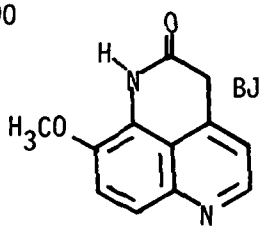
(500 mg)
BJ34081



BJ34063

6.5/6.1

(500 mg)
BJ34063



BJ34296

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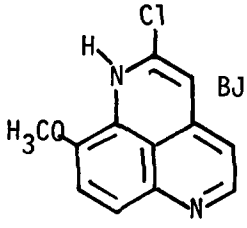
(500 mg)
BJ34296



BJ34072

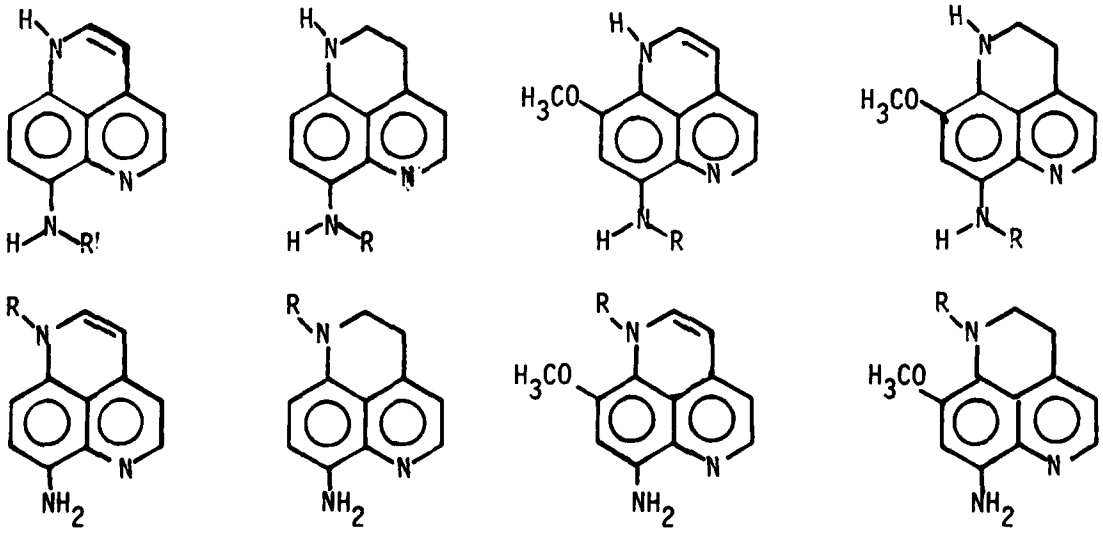
6.4/6.1

(500 mg)
BJ34072

2. No actual target compounds have been submitted to date although we appear to be only two trivial steps from the target compounds. Since the chemistry in the diazaphenalene series is new it has been designed to develop the best methods for entry into both the 9H and 9-methoxy diazaphenalenes before preparation of derivatives is begun.

B. WORK IN PROGRESS

1. Eventual Type of Target Compounds

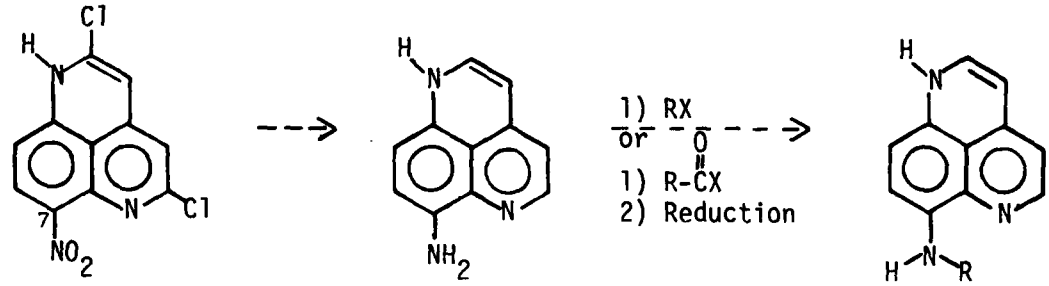


Series A
R = antimalarial effective side chain

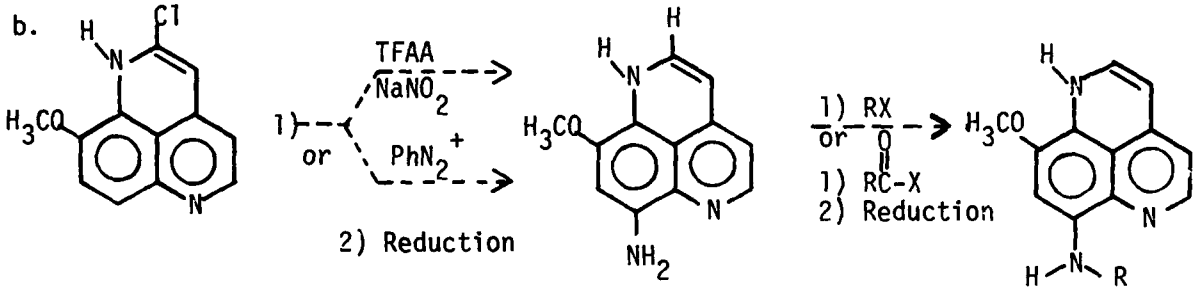
Series B
R = antimalarial effective side chain

Immediate Goals:

a.

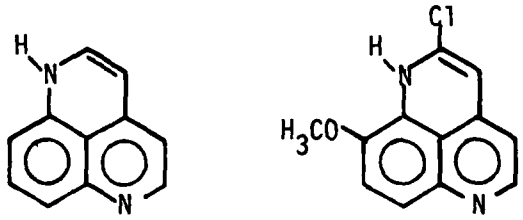


b.



The chemistry required to functionalize 1,6-diazaphenalene at the 7-position is now in hand and will be employed to prepare the target compounds.

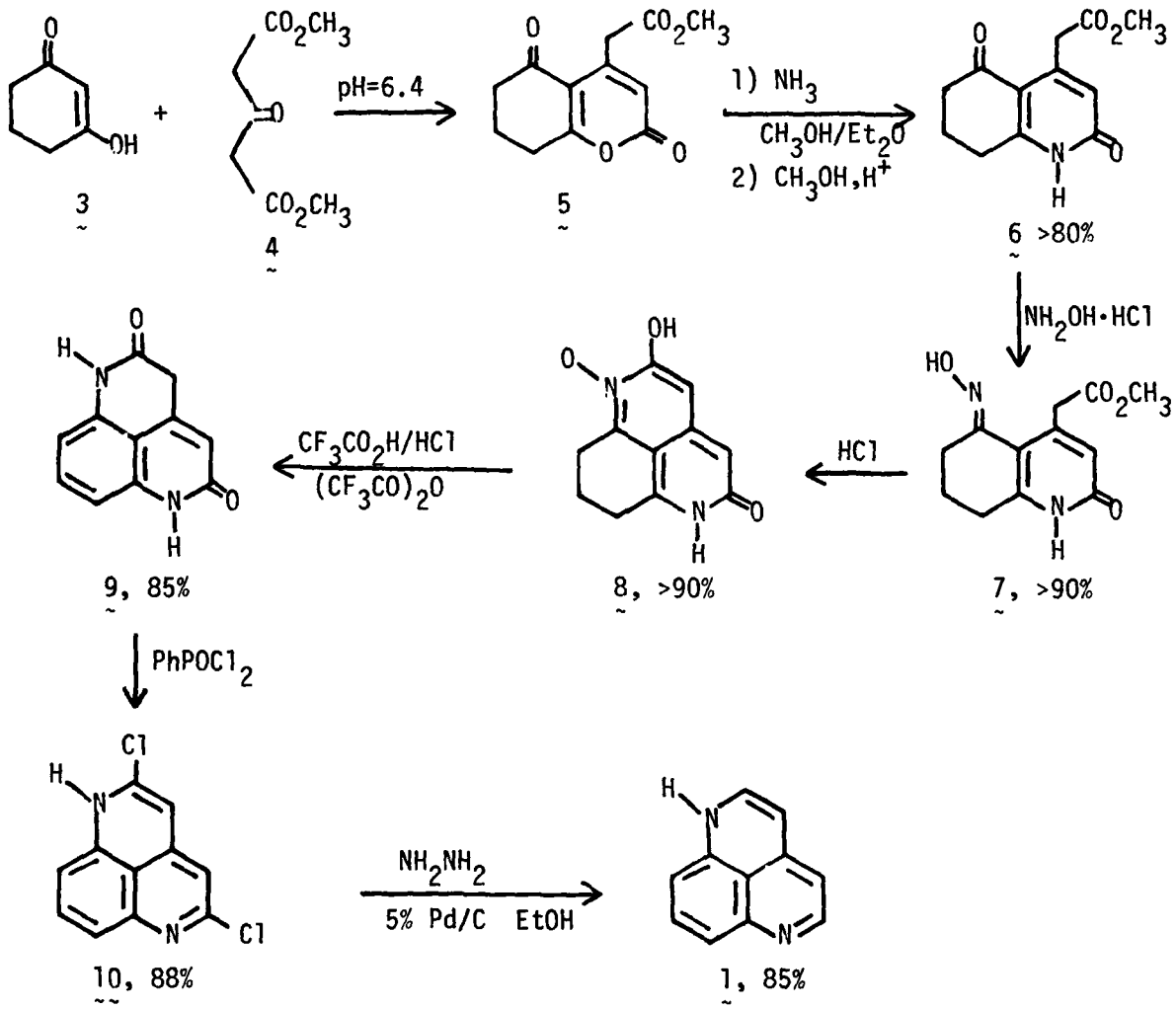
The synthesis of 1,6-diazaphenalene 1 and 2-chloro-9-methoxy-1,6-diazaphenalene 2 has required the use of chemistry which has no direct literature precedent (1,6-diazaphenalene is a new heterocycle); consequently, a good deal of development work had to be done in order to maximize the yields in both these series. This has held up progress. Despite this, entry into both ring systems has been achieved, and the reactions can be carried out on a practical scale.



1 2

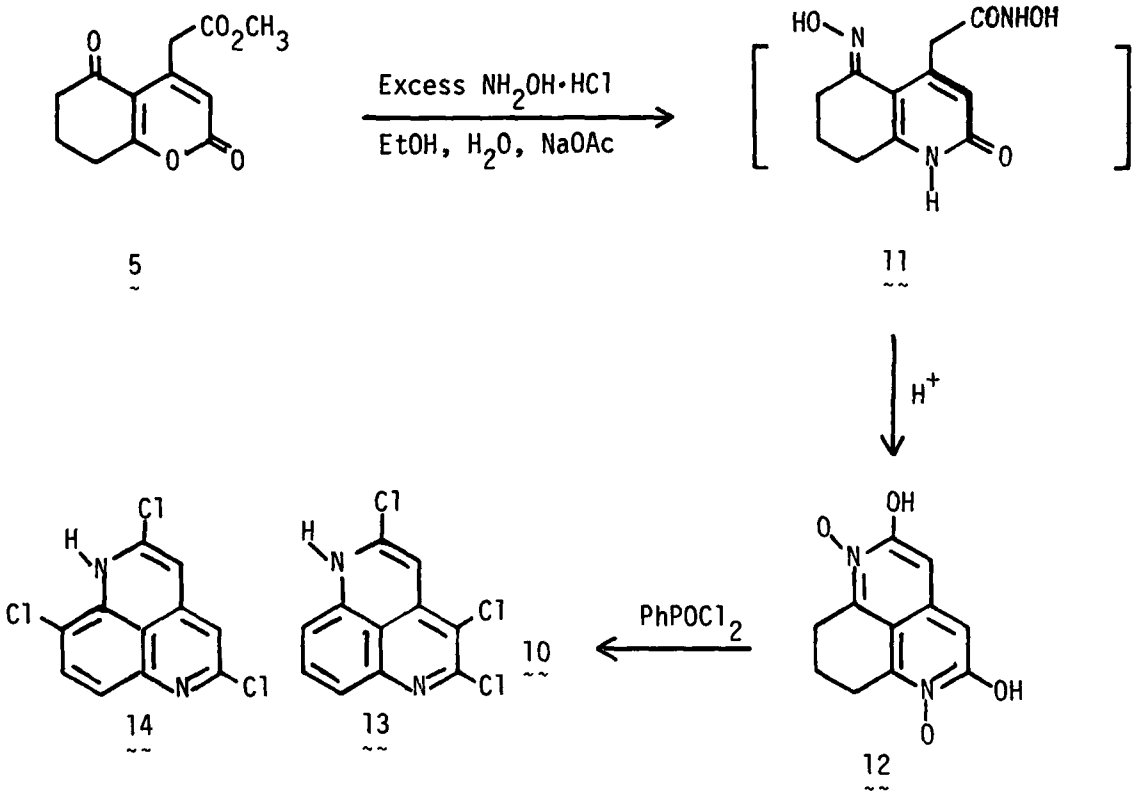
The synthetic work directed toward the synthesis of 1,6-diazaphenalene 1[1,2] and its 7-nitro derivative[3] has recently been reported. In 1977 cyclohexane-1,3-dione 3 was reacted with dimethyl β-ketoglutarate 4 in aqueous buffer to provide a good yield of the tetrahydrocoumarin 5 which was converted to the N-oxide 8 via intermediates 6 and 7, respectively (see Scheme I). The yields were high in all these steps and we were gratified to find that the crucial conversion of the quinolone N-oxide 8 to the desired 1,6-diazaphenalone 9 could be carried out by heating 8 in a mixture of $CF_3COOH/(CF_3CO)_2O/HCl$. The trifluoroacetic anhydride is crucial to this reaction for the formation of an N-O-trifluoroacetate bond facilitates the cleavage of the N-O bond allowing the modified[4]

SCHEME I



Semmeler-Wolff reaction to occur under very mild conditions. This is a tremendous improvement over the traditional method (Ac_2O) and gave better than 85% yield of nearly pure 9. The diazaphenalone 9 was then heated in phenylphosphonic dichloride[5] to provide the 2,5-dichloro-1,6-diazaphenalene 10 in 88% yield. Several different reduction procedures were attempted to convert 10 to 1, however, only one of these (NH_2NH_2, Pd/C) was found to be practical (see Scheme I). In 1979 the last five reactions in Scheme I were scaled up from 10 to 100 gram levels, moreover, work continued in order to develop even shorter, more practical routes to 1. It had been discovered (Annual Report, 1978) that the tetrahydrocoumarin 5 could be converted to the bis N-oxide 12 via the intermediate 11 in two trivial steps in greater than 90% yield, as illustrated in Scheme II. Treatment of the bis N-oxide 12 directly with phenylphosphonic dichloride gave a mixture of the three chlorinated 1,6-diazaphenalenes 10, 13 and 14 which was an exciting result. This sequence provided a shorter route to the diazaphenalene parent ring system for it eliminated the Semmler- lff ster and also permitted use of 5 in place of the 2-quinolone 6.

SCHEME II

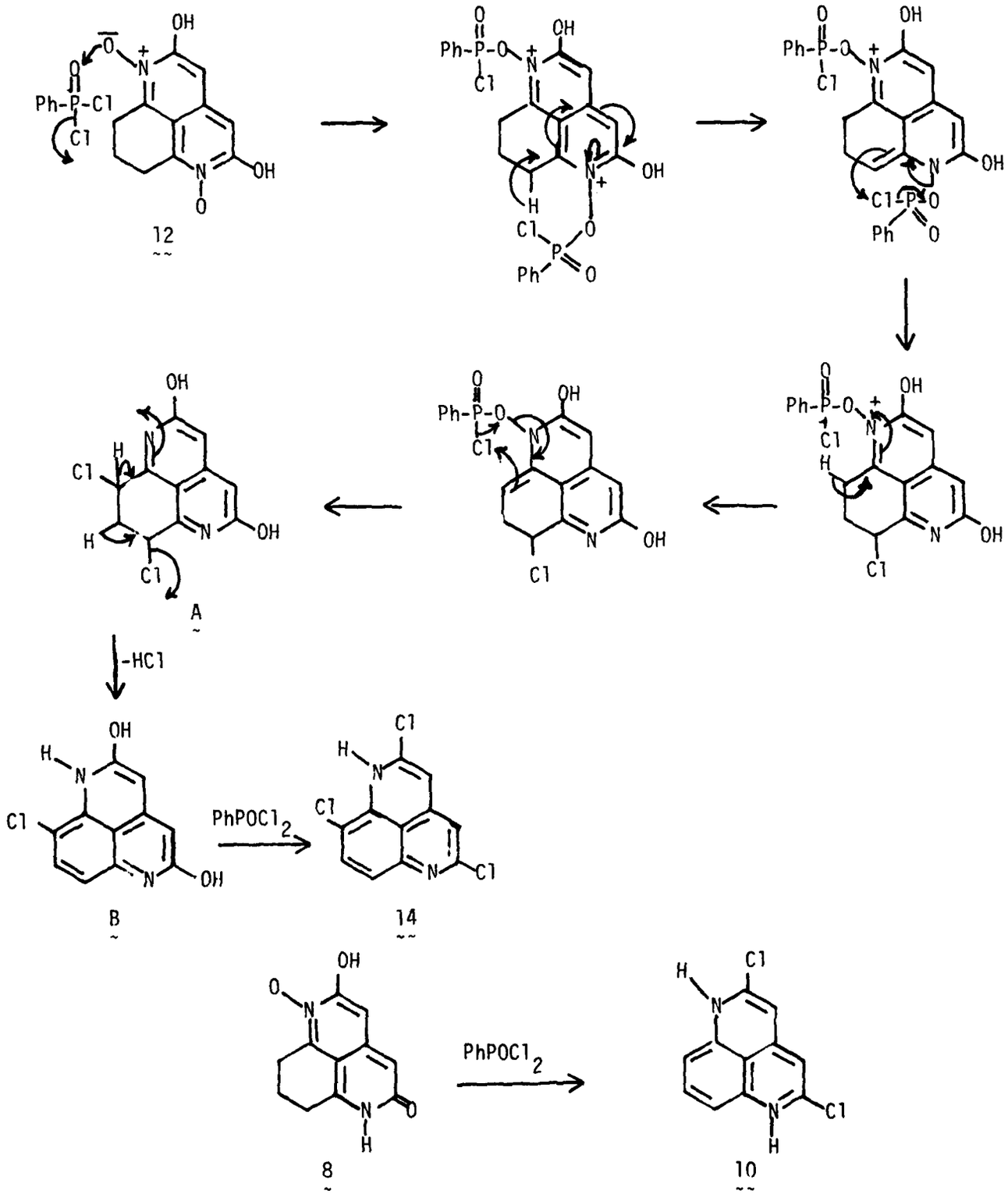


Yields	35%	24%	5% (based on NMR)
	17%	12%	2% (based on isolation)

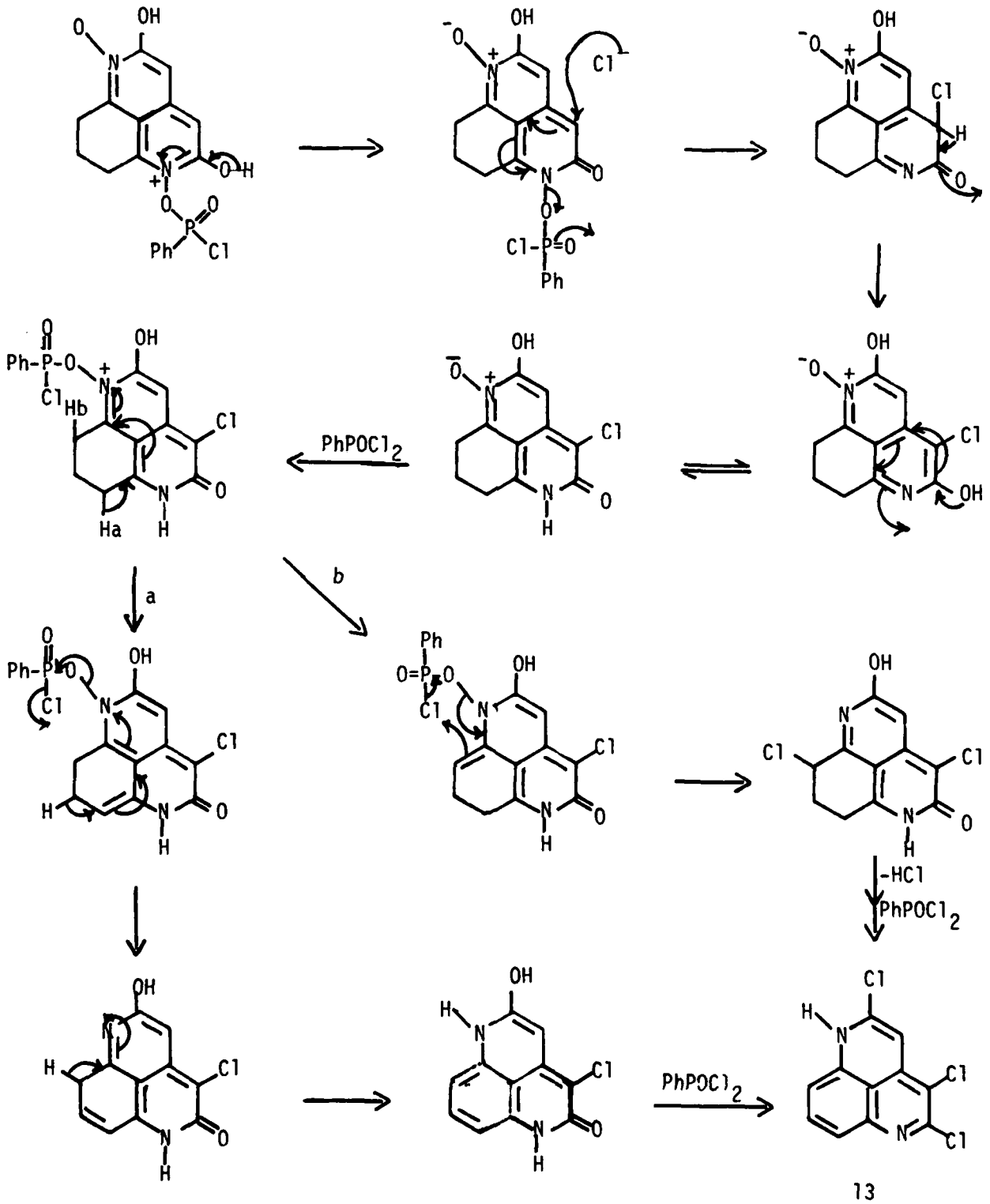
Examination of the possible mechanism for incorporation of three chlorine atoms into 13 and 14 (see Schemes III and IV) led to the realization that phenylphosphonic dichloride was involved in the aromatization step in much the same manner as trifluoroacetic acid in the modified Semmler-Wolff reaction. In the case of the bis-N-oxide 12, it is proposed that the N-oxide attacks the phenylphosphonic dichloride to expel the chlorine anion (see Scheme III) followed by an intramolecular rearrangement of the chlorine atom which had remained on phosphorous. This same sequence of steps is expected to occur at the second N-oxide function to generate a dichloro compound A. Loss of hydrogen chloride from A would provide 9-chloro-2,5-dihydroxy-1,6-diazaphenalene B which would then be converted to the trichloro compound 14 via routine transformations. A similar series of transformations can be employed to explain the origin of 13 in the same reaction mixture (see Scheme IV).

Based on the mechanistic study, a significant improvement could now be made in the route to 1,6-diazaphenalene 1. The mono N-oxide 8 was simply heated in phenylphosphonic dichloride to provide a 77% yield of 2,5-dichloro-1,6-diazaphenalene 10 which bypassed completely the Semmler-Wolff step. Furthermore, the product was homogeneous enough to be used in the next step after only minor purification. This reaction can now be carried out on the 50-100 gram scale in our laboratory.

SCHEME III



SCHEME IV



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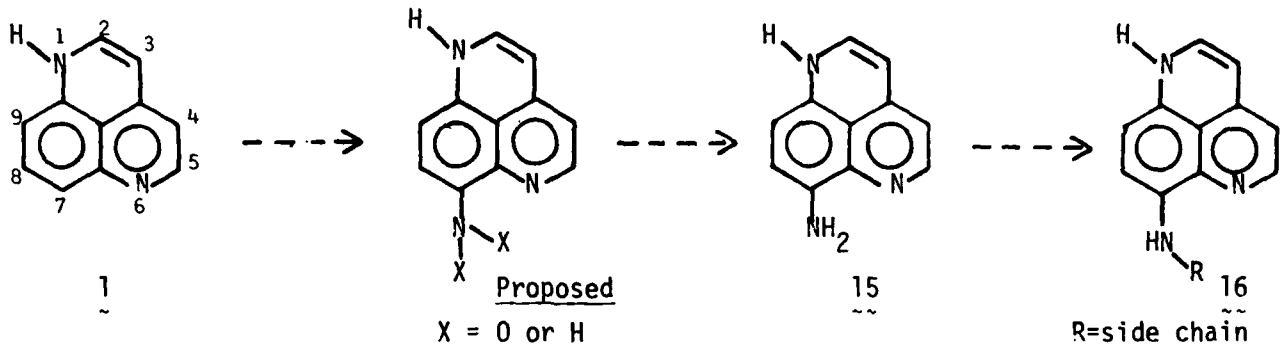
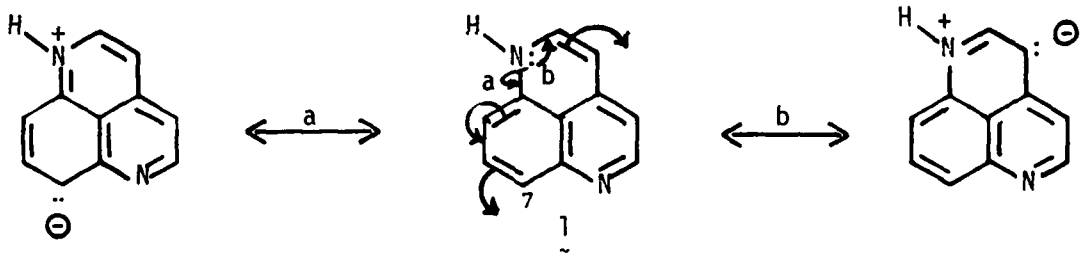
With the synthesis of 1 now well in hand, attention was turned to incorporation of the nitrogen function into position-7 of 1,6-diazaphenalene in order to permit preparation of the target compounds via the proposed sequence:

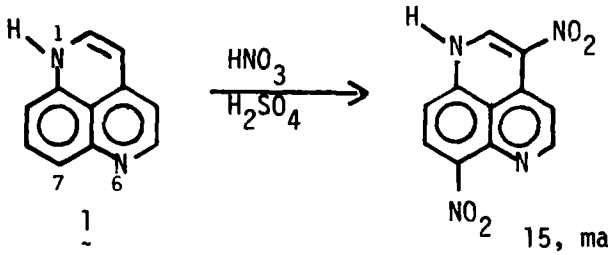


The most obvious method to accomplish this goal (finally successful) was by way of reagents which are a source of $+NO_2$. Electrophilic addition reactions to diazaphenalenes were without precedent and many reactions had to be attempted before success was achieved. Although the 7-position (a) of 1 would be expected to be active, examination of resonance structures demonstrated that position-3 (b) was also electron-rich and this latter property was a source of difficulty for some time.



Many nitration reactions were attempted at different temperatures and at different concentrations of $+NO_2$, and a few of these are illustrated in Scheme V. In general, reactions of 1,6-diazaphenalene 1 with one equivalent of nitric acid in either sulfuric or acetic acid gave 3,7-dinitro-1,6-diazaphenalene 15 as the major (isolable) product accompanied by starting material and dimeric material. When 1,6-diazaphenalone 9 was treated in a similar manner, the trinitro derivative 18 was produced, however, the other products were present in numerous numbers and rendered this reaction quite impractical. In order to work with compounds which would have a less complex NMR spectrum, and to take advantage of the kinetic deactivation properties of the chlorine atom, the next series of nitrations were carried out on 2,5-dichlorodiazaphenalene 10. The results with nitric acid, dissolved in either acetic acid or sulfuric acid, were unsatisfactory except for a trace of a mononitro derivative 17 isolated from the acetic acid medium.

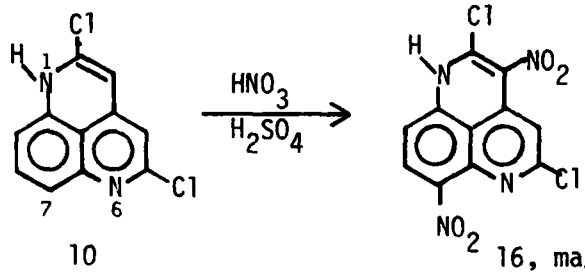
Even though the dinitro derivatives were always the principal component of these mixtures, the propensity for substitution at position-7 of 1 or 10 was encouraging for it was felt a mild source of E^+ might be utilized to



+ dimer + other compound + 1

1 15, major component

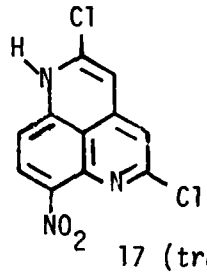
1 $\xrightarrow[H_2SO_4]{HNO_3}$ 15, major component + second dinitro compound + dimer + 1



+ dimer + second dinitro isomer

10 16, major component

10 $\xrightarrow[HOAc]{HNO_3}$ 16, major component + dimer +

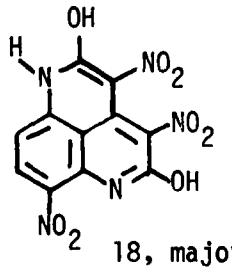


17 (trace)

10 $\xrightarrow[NaNO_2,\ 30°C]{CF_3CO_2H}$ 16, major component + 17, ~10%

10 $\xrightarrow[1/2\ NaNO_2,\ -23°C]{CF_3CO_2H}$ 17, 22-30% + dimer + 10 + small amount of 16

9 $\xrightarrow[HNO_3]{H_2SO_4}$



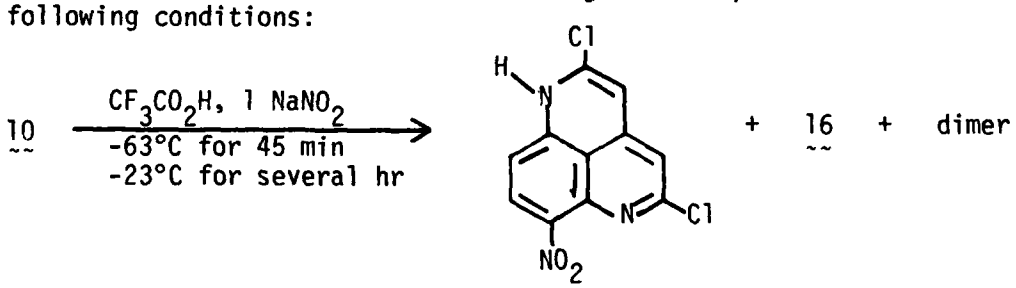
+ 3-4 other compounds

18, major product

9 $\xrightarrow[AcOH]{HNO_3}$ 18, major product + 3-4 other compounds

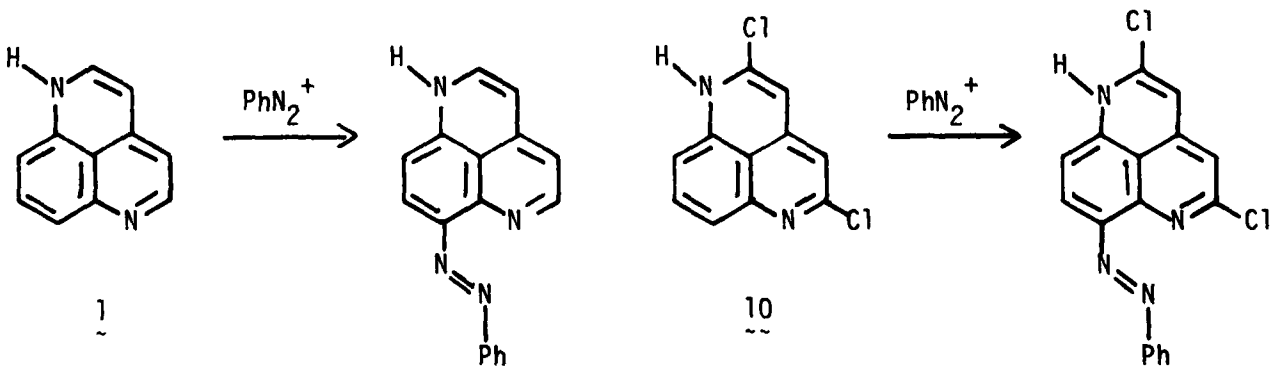
differentiate between the reactivity of these positions. Efforts were made to find less reactive electrophiles for this purpose, and the use of +NO or PhN_2^+ seemed a reasonable alternative to $+NO_2$. Stewart[6] reported in 1974 that +NO might well be an intermediate in the nitration of toluene with sodium nitrite in the presence of trifluoroacetic acid, therefore, attempts were made to use this procedure in the 1,6-diazaphenalene area. Immediately we began to observe better results. When the nitrite and trifluoroacetic acid were reacted with 10 at 30°C about a 10% yield of 7-nitro-2,5-dichloro-1,6-diazaphenalene 17 was observed as shown in Scheme V. If the molar equivalent of nitrite was reduced to 1/2 equivalent and the temperature of the reaction reduced to -23°C, a 22-30% yield of 17 was obtained, in addition to recovered starting material.

To date, the best yield of 7-nitro-2,5-dichloro-1,6-diazaphenalene 17 (40-50%, 60% based on recovered starting material) was obtained under the following conditions:



17, 40-50% yield

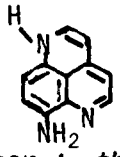
Although it is now believed[7] that the TFAA/$NaNO_2$ reaction does not go through +NO, the method is quite useful for preparation of 17. We are now trying to find a means with which to run the nitration at -90°C to further increase the ratio of mononitro/dinitro. Along similar lines (weak E^+) in a parallel study, both 1,6-diazaphenalene 1 and 2,5-dichlorodiazaphenalene 10 gave only products of monosubstitution 19 and 20, respectively, when stirred with phenyldiazonium chloride[8] at 0°C. Although the mass spectral and NMR data support the structures of 19 and 20, these compounds must be completely characterized and then converted to the desired amine 15 (see Methods of Procedure Section).



1 10 19 20

We have recently attempted to reduce 17 to the desired 7-amino-1,6-diazaphenalene 15 with hydrazine over Pd/C in similar fashion to work completed in our laboratory

17 →

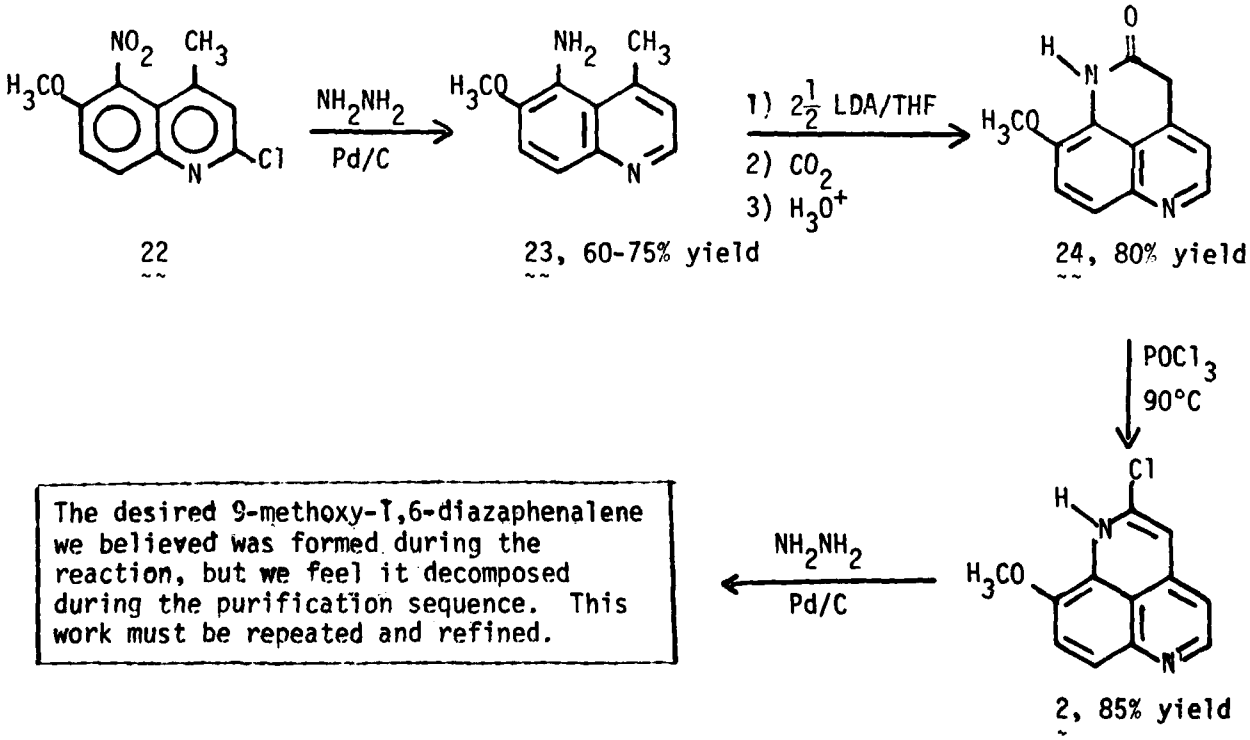


15

last year in the 9-methoxy-diazaphenalene series. The NMR spectrum of the crude material indicated the chloro groups had been removed while the IR spectrum no longer contained bands for a nitro group. While these results are encouraging, they are far from convincing. This work will be repeated and scaled up!

While the work toward 7-amino-1,6-diazaphenalene 15 was being performed, Robert Weber has continued his efforts to prepare 9-methoxy-1,6-diazaphenalene 21. In the past year the synthesis of the 2-chloro-5-nitro-6-methoxyquinoline 22 has been scaled up and it has been converted in yields varying from 60 to 75% to 4-methyl-5-amino-6-methoxyquinoline 23 (Scheme VI). The carbonalation of 23 to provide 9-methoxy-1,6-diazaphenalone 24 has now been carried out on gram quantities, essentially in a "one-pot" reaction procedure. Conversion of 24 to the desired 2-chloro-9-methoxy-1,6-diazaphenalene 2 was difficult; however, careful control of the reaction temperature (90°C) of the $POCl_3$ medium gave consistently 80-85% yields of the desired chloro compound 2. The simple hydrazine, Pd/C reduction procedure employed in our previous work gave two new compounds on TLC, however, decomposition occurred during the chromatography step. This one step must be repeated and refined until it is a useful reaction in this preparation!

SCHEME VI



22

23, 60-75% yield

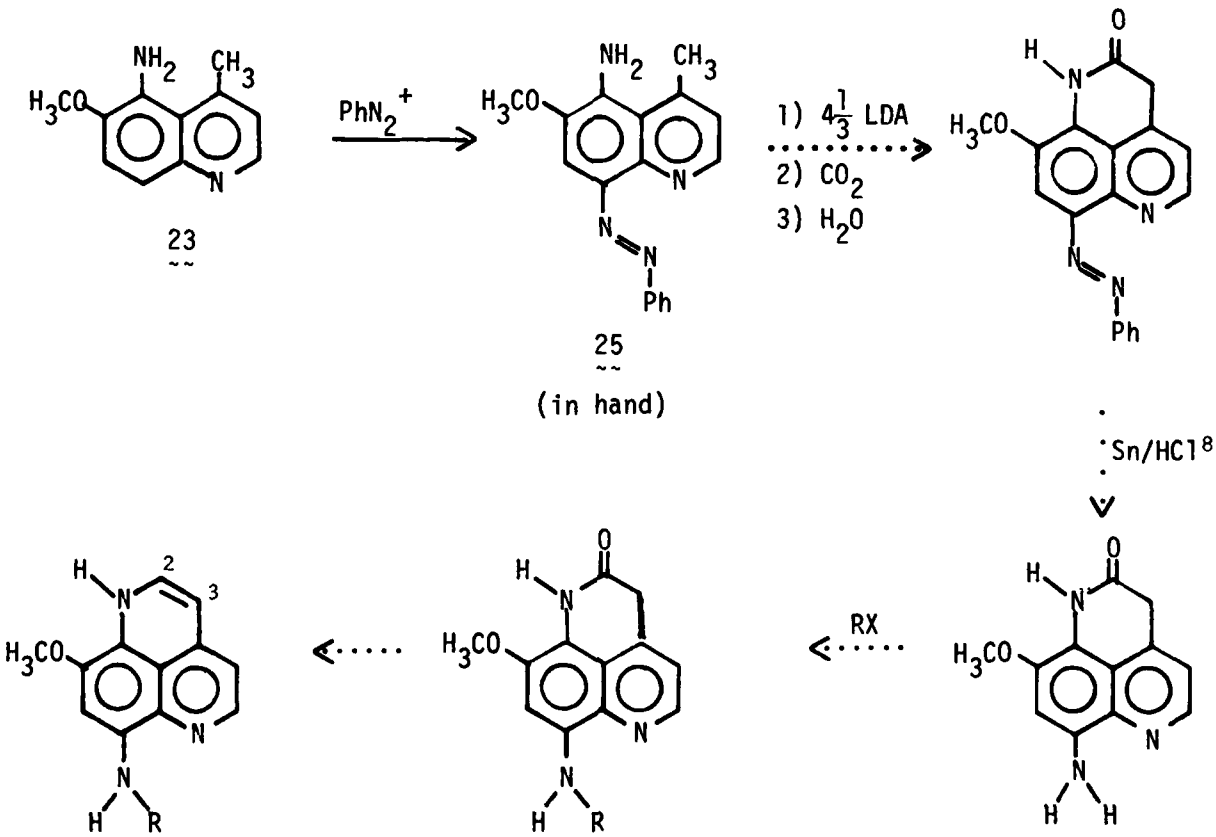
24, 80% yield

2, 85% yield

The desired 9-methoxy-1,6-diazaphenalene we believed was formed during the reaction, but we feel it decomposed during the purification sequence. This work must be repeated and refined.

There are several methods for incorporation of the 7-amino group into the 9-methoxy-1,6-diazaphenalene ring system to provide the desired template for alkylation with the antimalarial-active side chains. One of these is the nitration of molecules such as 2 and 24; however, cleavage of the O-CH_3 bond might prove to be a problem. For this reason we have attempted to react phenyldiazonium chloride with the 5-aminoquinoline 23[8] and the success of this venture is quite promising. The desired red-colored azo compound 25 was formed from 23 in 70% yield, as illustrated in Scheme VII. We are now in the process of carbonylating the 4-methyl function (see below) by the method shown earlier in Scheme VI.

SCHEME VII

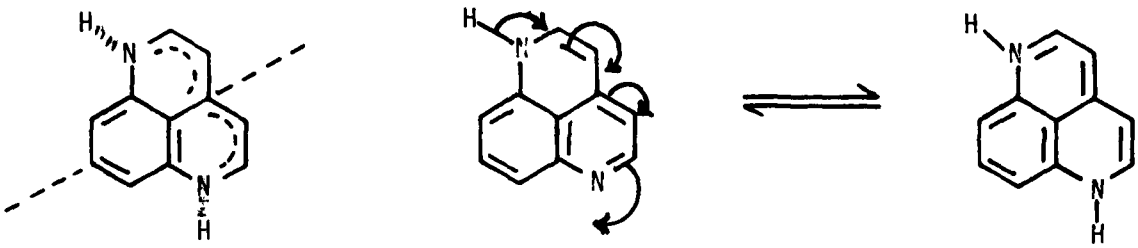


Eventual target with and without a 2,3-double bond.

Dotted arrows indicate proposed reactions.

Characteristics of 1,6-Diazaphenalene//Drug Potential. Since early in 1979 access[2] to pure samples of 1,6-diazaphenalene 1 has permitted examination of some of its properties vis a vis potential as a drug in the antimalarial area. The diazaphenalene 1, itself, is a very polar compound (R_f = 0.076 on SiO_2, 20% triethylamine-methanol) examination of whose NMR spectrum clearly indicates that the proton transfer between the two nitrogen atoms is faster

than the NMR time scale. The set of NMR signals more closely fit a spectrum for 1 than the spectrum expected for 1a or 1b.



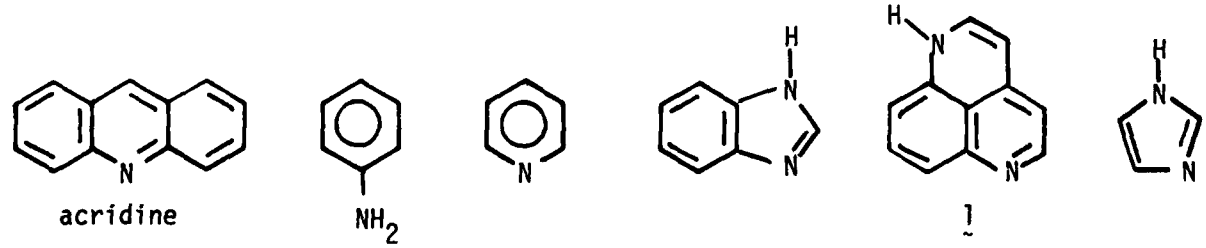
1 1a 1b

plane of symmetry

This phenomenon is characteristic of the biologically important base imidazole and has prompted our contention that 1 is a vinylogous imidazole.[2] In this vein there are two properties of 1 that need to be discussed: water solubility/lipophilicity and acidity. It has been gratifying to find that even though 1 resembles imidazole in terms of spectroscopy, the water solubility much more clearly resembles quinoline. Imidazole is very soluble in water while 1,6-diazaphenalene is only slightly soluble (~20 mg/1000 ml H_2O) in the same medium. Consequently the lipophilicity of 1,6-diazaphenalene is somewhat closer to quinoline, and this appears to be an important property in terms of drug transfer across cell membranes.

The pK_a data for 1,6-diazaphenalene, however, completely supports our previous contention that 1 is a vinylogous imidazole (see reference 2). Examination of the data in Figure 1 demonstrates that 1 (pK_a = 6.56 in H_2O) has a value much closer to imidazole (pK_a = 6.89 or 6.95 in H_2O) than quinoline (pK_a = 4.9) or benzimidazole (pK_a = 5.48).

FIGURE 1



	acridine	NH_2			1	
pK_a	5.6	4.7	5.2	5.48	6.56	6.89 6.95

The pK_a for 1,6-diazaphenalene was determined by potentiometric methods.

Experimental

Microanalyses were performed on an F & M Scientific Corp. Carbon, Hydrogen, Nitrogen Analyzer Model 185. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on Varian T-60 and CFT-20 spectrometers with Me_4Si internal standard. All mass spectra were taken on either a Hitachi Perkin-Elmer RMU-6 or AEI MS 902 instrument. Infrared spectra were obtained on a Beckman IR-8 in either chloroform or KBr. Analytical TLC was performed on EM precoated sheets, silica gel F-254, 0.25 mm thickness while column chromatography was carried out with Baker Analyzed silica gel 60-200 mesh. Some IR spectra were recorded on a Beckman Acculab 1 spectrometer.

Dimedone, cyclohexane-1,3-dione, dimethyl β-ketoglutarate, and N-benzylamine were purchased from Aldrich Chemical Co. The citrate-phosphate buffer (pH 5.5) was prepared by dissolving $Na_2HPO_4 \cdot 7H_2O$ (2.60 g) and citric acid (0.82 g) in water (200 ml).

Preparation of 2,3,5-trichloro-1,6-diazaphenalene 13 and 2,5,9-trichloro-1,6-diazaphenalene 14. To 7,8-Dihydro-2,5-dihydroxyl-1,6-diazaphenalene-1,6-dioxide 12 (1.17 g, 0.005 mol) phenylphosphonic dichloride (10 ml) was added and the suspension heated under reflux (oil bath), the temperature of which was raised from 25°C to 80°C over a 30 min period. Gentle evolution of HCl then began and the bis-N-oxide began to dissolve. After 20 min, the bath temperature was increased to 98°-100°C for 10 hrs, and then heated at 118°-120°C for 3 additional hrs. The reaction mixture was worked up (NH_4OH/H_2O) as described in the next procedure for 2,5-dichloro-1,6-diazaphenalene. The product obtained was a light yellow solid which contained two major components and one minor component present in less than 6 % yield, as indicated by TLC.

These two compounds were separated by column chromatography (silica gel, eluent; benzene, chloroform). The first fraction provided 2,5,9-trichloro-1,6-diazaphenalene 14 (0.23 g, 17%) as a yellow powder: mp 218-220°C (dec); IR (KBr) 3370(s), 1625(s), 1605(s), 1360(m), 1124(s), 830(s) and 780(m) cm^{-1}; NMR (CF_3COOH, 220 MHz) δ 5.86(s,1H), 5.89(s,1H), 6.49(d,1H,J=9 Hz), and 7.04(d,1H, J=9 Hz); CI mass spectrum (NH_3) m/e (rel intensity); 275(26), 273(86), 271(M+1,100).

Anal. Calcd. for $C_{11}H_5N_2Cl_3$: C, 48.62; H, 1.84; N, 10.33. Found: C, 48.96; H, 1.61; N, 10.34.

The second fraction contained 2,3,5-trichloro-1,6-diazaphenalene 13 (0.16 g, 12%) isolated as a yellow powder: mp 228-230°C (dec): IR (KBr) 3200-2800 (broad bands), 1630(s), 1600(s), 1580(sh), 1360(s), 1350(s), 1235(s), 1130(s), 810 and 760 cm^{-1}; NMR (CF_3COOH, 220 MHz) δ 6.08(s,1H), 6.48(d,1H, J=8.5 Hz), 6.50 (d,1H,J=8.5 Hz), 6.99 (t,1H,J=8.5 Hz); CI mass spectrum (NH_3) m/e (rel intensity), 275(27), 273(79), 271(M+1, 100).

Anal. Calcd. for $C_{11}H_5N_2Cl_3$: C, 48.62; H. 1.84; N, 10.33. Found: C, 47.51; H, 1.59; N, 9.30. The yields of these two products by NMR and by TLC were considerably higher (approximately 40% and 20%), however, separation of the components was quite difficult and further work is necessary to improve the isolated yields of these two materials. Later fractions contained a 5 % yield of 1,6-diazaphenalene 1.

Preparation of 2,5-Dichloro-1,6-diazaphenalene (10) from 7,8-Dihydro-2,5-dihydroxy-1,6-diazaphenalene-1-oxide (8). A mixture of 7,8-dihydro-2,5-dihydroxy-1,6-diazaphenalene-1-oxide 8 (4.36 g, 0.02 mol) and phenylphosphonic dichloride (30 ml) was heated under reflux in an oil bath, the temperature of which was raised from room temperature to 95°C over a 30 min period. Gentle evolution of hydrogen chloride then began and the N-oxide began to dissolve. After the starting material had dissolved the mixture was held at 95-100°C for 12 hrs and then at 120-125°C for 3 hrs. The mixture was cooled and added with stirring to ice water. Decomposition of the dark reaction mixture with water gradually produced a tarry residue and yellow crystals. The yellow crystals, contaminated with decomposition products of excess reagent and of phenylphosphonic anhydride,were filtered from the solution and the filtrate was then basified with concentrated ammonium hydroxide. This furnished more of the yellow solid. The precipitate was collected by filtration, washed with H_2O and air-dried; yield 0.93 g. The tarry mass was triturated with concentrated NH_4OH, the yellow precipitate which was isolated was separated by filtration, to provide a second crop of dichloro compound which was washed and dried as above, combined weight 2.74 g; total yield 3.67 g (77%). Properties of this compound were reported in the annual report (TLC and IR identical to the authentic sample whose preparation was described in our annual report, 1978).

2,5-Dichloro-1,6-diazaphenalene (10) - Scale-up. The Semmler-Wolff reaction product, 2,5-dioxo-3H-1,6-diazaphenalene (9, 16.0 g, 0.08 m) was dissolved in phenylphosphonic dichloride (80 ml, an excess). The reaction was heated gradually (with stirring) to a temperature of 90-100°C and held there for 30 min. The reaction was heated to 120-125°C for 3 hrs. The solution was then cooled and poured onto ice-cold water (300 ml) followed by stirring at room temperature for 2 hrs. The solid which precipitated was washed in succession with water, aqueous ammonia (1:1), water and then crystallized from hot aqueous ethanol (70%). The yellow-green crystals (10, 15 g, 79% yield) had a melting point of 223-225°C: IR (KBr) 3400(w, sharp in $CHCl_3$), 1640, 1590, 1470, 910, 820 and 770 cm^{-1};NMR (220 MHz, CF_3COOH) δ 6.52 (2H,s), 7.28(2H,d,J=8 Hz) and 7.88 (1H,t,J=8 Hz); mass spectrum (70 ev) m/e (rel intensity) 240 (12), 238 (62), 236 (M^+, 100), 200 (58), 165 (50), CI mass spectrum (NH) 238 (64), 237 (M+1, 100), 236 (M^+, 30). An additional 1.3 g of 10 were obtained by chromatography of the mother liquor obtained after crystalization.

Anal. Calcd. for $C_{11}H_6Cl_2N_2$: C, 55.69; H, 2.53; N, 11.81; Cl, 29.96. Found: C, 55.96; H, 2.78; N, 11.74; Cl, 30.26.

1,6-Diazaphenalene (1) - Scale-up. The 2,5-dichloro-1,6-diazaphenalene (10, 7.0 g, 0.03 m) was dissolved in absolute ethanol (300 ml) followed by addition of palladium on carbon (2.5 g, 5%). Hydrazine [85 ml of 95% material in ethanol (85 ml)] was added portionwise at reflux over a five-hour period (at this point TLC indicated the absence of starting material). The reaction was refluxed for 12 additional hrs followed by removal of the catalyst by vacuum filtration. The solvent was removed from the mother liquor under reduced pressure to provide a yellow-green solid which was washed in succession with water, aqueous sodium carbonate and water. The combined washings were basified with aqueous sodium carbonate to provide 1,6-diazaphenalene (1 4.5 g). An additional amount of diazaphenalene (1, 0.3 g) was obtained when the filtrate was allowed to stand overnight. The combined yield of crude product (1, 96% yield) was 4.8 g and this material was chromatographed on

silica gel (gradient elution, benzene/chloroform/ethylacetate/methanol) to provide an 88% yield of 1,6-diazaphenalene 1: mp 220-222°C, IR (KBr) 3280, 3200, 1620, 1580, 1470; NMR (CD_3OD, 220 MHz) δ 5.95 (2H,d,J=6 Hz), 6.70 (2H, d,J=8.5 Hz), 7.30 (1H,t,J=8.5 Hz) and 7.42 (2H,d,J=6 Hz); mass spectrum (CI, NH_3) m/e (rel. intensity) 169 (M+1, 100), 168 (29), 167 (12).

Anal. Calcd. for $C_{11}H_8N_2$: C, 78.55; H, 4.79. Found: C, 77.87; H, 5.12.

Note. 1,6-Diazaphenalene is soluble in polar organic solvents more so than their nonpolar counterparts. A solubility scheme (approximate) appears to follow this order: EtOH>MeOH>EtOAc>Bz>$CHCl_3$>Et_2O (least soluble).

Attempted Mononitration of 1,6-Diazaphenalene 1 with Nitric Acid/Acetic Acid. 1,6-Diazaphenalene 1 (0.5 g, 0.0029 m) was dissolved in acetic acid (6 ml) and a nitric acid (0.0029 m)/acetic acid mixture was added with stirring over a period of 15 min (room temperature). The mixture was then warmed to 60°C for 5 min followed by an additional stirring for 1 1/2 hr at room temperature. When the solution was diluted with water, a solid precipitated which was filtered from the medium and was washed with water. The aqueous layer was evaporated to dryness to furnish the same solid. The total solids (0.75 g) were combined and TLC indicated that at least four different compounds were present in this crude mixture.

The solid was subjected to preparative TLC (silica gel, eluent - 50% ethylacetate, chloroform) which permitted isolation of only two compounds. The spectra of both of these compounds had an M^+ of 258 which indicated that they were isomers of dinitro-1,6-diazaphenalene.

3,7-Dinitro-1,6-diazaphenalene 15, NMR (220 MHz) CD_3OD δ 7.42(d), 7.97(d), 8.13 (d), 8.66 (d) and 9.48 (s); mass spectrum (CI, NH_3) 260 (19), 259 (M^++1, 100%).

Second dinitro compound gave the same mass spectrum -- we are trying to obtain more of the compound for NMR, IR, CHN data at present.

The same result was obtained when the nitration of 1,6-diazaphenalene was carried out in a mixture of HNO_3/H_2SO_4 at ice bath temperature.

Attempted Mononitration of 2,5-Dihydroxy-1,6-diazaphenalone 9 with HNO_3/H_2SO_4. The diazaphenalone 9 (2.0 g, 0.01 m) was added over a 30 min period to sulfuric acid (10 ml,sp gr 1.84) cooled to ice bath temperature. Nitric acid (70%, 0.97 ml, 0.0114 m) was added dropwise to the solution over a period of 1 hr with cooling. The mixture was stirred for an addition 1 hr at room temperature and then poured onto ice (100 g) at which time a yellow solid precipitated from the medium. The precipitate was filtered from the medium, washed with water and dried to provide one gram of material which was not homogeneous (TLC indicated the presence of four components). The major component 18 of this mixture was purified by preparative TLC (silica gel, eluent 5% methanol/chloroform): mp >300°C, IR (KBr) 3475, 1630, 1600, 1530, 1470, and 1240 cm^{-1}; NMR (220 mHz) CD_3OD δ 6.99 (d,1H,J=10 Hz), 8.36 (d,1H, J=10 Hz); mass spectrum 336 (35), 335 (100).

Attempted Mononitration of 2,5-Dichloro-1,6-diazaphenalene 10 with HNO_3/AcOH. The 2,5-dichloro-1,6-diazaphenalene 10 (0.5 g, 0.0021 m) was dissolved in acetic acid (15 ml) and stirred at room temperature. A mixture of acetic acid and nitric acid (equivalent to 0.0021 m HNO_3) was added dropwise and the reaction mixture was stirred at room temperature for 1 hr. The solution which resulted was poured into cold water (100 ml) and the precipitate which formed was filtered from the medium. The solid was washed with water and dried to provide a yellow solid (560 mg): mp 135-140°C. Thin layer chromatography indicated the presence of four components in the mixture, while the mass spectrum contained ions at mass values consistent with both mono and dinitro substitution reactions.

The crude solid was chromatographed on silica gel (eluent - benzene/chloroform, gradient elution) to furnish a yellow solid (50 mg) which was recrystallized from methanol: 3,7-dinitro-2,5-dichloro-1,6-diazaphenalene 16; mp 230°C; NMR (220 mHz) $CDCl_3$ δ 6.79 (s,1H), 4.43 (d,1H,J=10 Hz) and 8.55 (d, 1H,J=10 Hz).

Preparative TLC was necessary to separate the other components from each other. From this purification step a dimer [M^++1, 470, CI, NH_3] was isolated which did not contain chlorine atoms according to the mass spectrum. Furthermore, a mono nitro-dichlorodiazaphenalene was obtained [M^++1 = 282 (100%) M^+ = 281, CI spectrum-NH_3] which may be 3-nitro-2,5-dichloro-1,6-diazaphenalene. Additional data are obviously required to make accurate structural assignments for the compounds formed in this reaction.

Attempted Mononitration of 2,5-Dichloro-1,6-diazaphenalene 10 with Nitrous Vapors. A solution of 2,5-dichloro-1,6-diazaphenalene 10 (2 g) in acetic acid (80 ml) was prepared. Nitrous vapors (from As_2O_3 and HNO_3) were bubbled through the mixture for 15 min after which time the solution was diluted with water and a precipitate formed. The solid was filtered from the medium, washed with water and dried to provide an amorphous brown precipitate. TLC indicated the presence of at least four compounds while a mass spectrum (CI, NH_3) of the solid did not have ions at mass values consistent with the presence of mono or dinitro compounds. Furthermore, no chlorine isotope pattern was observed in the mass spectrum. For the above reasons, the nitrous vapors approach was dropped.

Preparation of 7-Nitro-2,5-dichloro-1,6-diazaphenalene 17 with Sodium Nitrite in Trifluoroacetic Acid at -23°C. Dichlorodiazaphenalene 10 (6.0 g, 0.025 m) was dissolved in trifluoroacetic acid (100 ml) and cooled to -23°C (dry ice/CCl_4) with stirring. Sodium nitrite (876 mg, 0.0126 m) was added in one portion to the reaction and the solution was stirred for 5 hrs at -23°C (it solidified after 4 hrs). The temperature was gradually allowed to raise to room temperature and stirred at 26°C for 1 additional hr. The mixture was poured into cold water (800 ml) and left to stand at room temperature. A precipitate formed, was filtered from the medium, and was washed with water to provide a brown solid (4.0 g, TLC indicated the presence of four compounds). More of the same solid was obtained on extraction of the mother liquor with ethylacetate. The majority of the material from the organic layer corresponded to the material of highest R_f later proven to be 7-nitro-2,5-dichloro-1,6-diazaphenalene 17.

The solid (crude) was chromatographed on silica gel (gradient elution - chloroform/ethylacetate/methanol) to provide 7-nitro-2,5-dichloro-1,6-diazaphenalene 17 (1.55 g, 22% yield): mp = 233-235°C, IR (KBr) 3250, 3110, 1620,

1600, 1540, 1460, 1360, 1330, 1240, and 1090 cm^{-1}; NMR (220 mHz) CD_3OD δ 6.60 (s,1H), 6.61 (s,1H), 6.66 (d,1H,J=10 Hz), 8.25 (d,1H,J=10 Hz): NMR (60 mHz) TFAA δ 7.33 (s,2H), 7.66 (d,1H,J=10 Hz), 9.10 (d,1H,J=10 Hz); mass spectrum (CI, NH_3), 286 (9), 284 (58), 282 (M^++1, 100) therefore M^+ = 281 as expected for $C_{11}H_5N_3Cl_2O_2$.

Anal. Calcd. for $C_{11}H_5N_3Cl_2O_2$: C, 46.97; H, 1.78; N, 14.95. Found: C, 46.57; H, 1.62; N, 14.82.

Preparation of 7-Nitro-2,5-dichloro-1,6-diazaphenalene 17 with Sodium Nitrite in Trifluoroacetic Acid at -63°C. Dichloro-1,6-diazaphenalene 10 (6 g, 0.025 m) was dissolved in TFAA (100 ml) and stirred at -63°C (dry ice/chloroform). Sodium nitrite (1.75 g, 0.025 m) was added in one portion with stirring at -63°C and the mixture solidified after 45 min. The temperature was allowed to rise to room temperature and was maintained there for 30 min. The reaction was worked-up exactly as reported in the previous experiment to provide a brown solid (5.2 g). An additional two grams of solid were obtained on extraction with ethylacetate. When the residue (2 g) from the organic extract was triturated with warm methanol, pure 7-nitro-2,5-dichloro-1,6-diazaphenalene 17 (mp 231-235°C, dec.) was obtained.

The remainder of the solids (6.2 g) were chromatographed on silica gel (eluent - chloroform) to provide an additional 2.2 g of the mononitro compound 17 (total yield 3.0 g = 42%).

The residue from the column contained three to four compounds - starting material (~500 mg), mononitrodiazaphenalene 17 and some dimeric material yet to be identified.

Preparation of 7-Amino-1,6-diazaphenalene (15). The 7-nitro-2,5-dichloro-1,6-diazaphenalene 17 (0.5 g, 0.0017 m) was dissolved in ethanol (100 ml). Palladium on carbon (0.15 g of 5%) was added to the solution followed by dropwise addition of hydrazine hydrate (5 ml of 95% in ethanol, 5 ml) at reflux with stirring. After 30 min at reflux, thin layer chromatography indicated the absence of starting material. In order to ensure that the reaction was complete, two milliliters of hydrazine were added and the solution was refluxed for 30 min. The catalyst was removed by filtration and the solvent removed under reduced pressure. The residue was washed with aqueous sodium carbonate solution (4%) to provide a black solid (0.25 g) which was composed of a major component and two minor components as evidenced by TLC.

The crude material was separated by preparative TLC (silica gel, methanol) to provide an amorphous solid; IR indicated the absence of bands from a nitro group, the NMR spectrum indicated that both chlorine atoms had been lost, while the mass spectrum (CI) did not show a parent peak but did have a peak at 91.5 = $\frac{M+}{2}$; however, while these results are promising they are far from convincing at the moment.

Preparation of 7-Phenylazo-2,5-dichloro-1,6-diazaphenalene 20. Aniline (0.033 g, 0.003 m) was dissolved in hydrochloric acid (10 ml) and was diazotized with sodium nitrite [0.24 g, 0.003 m in H_2O (3 ml)] with chilling. A solution of 2,5-dichloro-1,6-diazaphenalene 10 (0.82 g, 0.0035 m) in acetic acid (6 ml) was diluted to 20 ml with water, chilled to about -10°C, and slowly treated

(with stirring) with the diazo solution. After stirring at -10°C for 45 min, the mixture was made alkaline with ammonium hydroxide. The brown precipitate was filtered off, and washed with water. A red-purple phenylazo compound 20 was separated from the solid by column chromatography (alumina-benzene-chloroform gradient elution): mp 224-226°C (dec.); IR (KBr) 3065 (w), 1610 (s), 1595 (sh), 1536 (s), 1338 (s), 1270 (s), 1128 (s) and 746 (s) cm^{-1}; CI mass spectrum (NH_3) m/e (rel. intensity): 345 (10), 343 (78), 341 (M+1 for mono-phenylazo derivative, 100) therefore M^+ = 340.

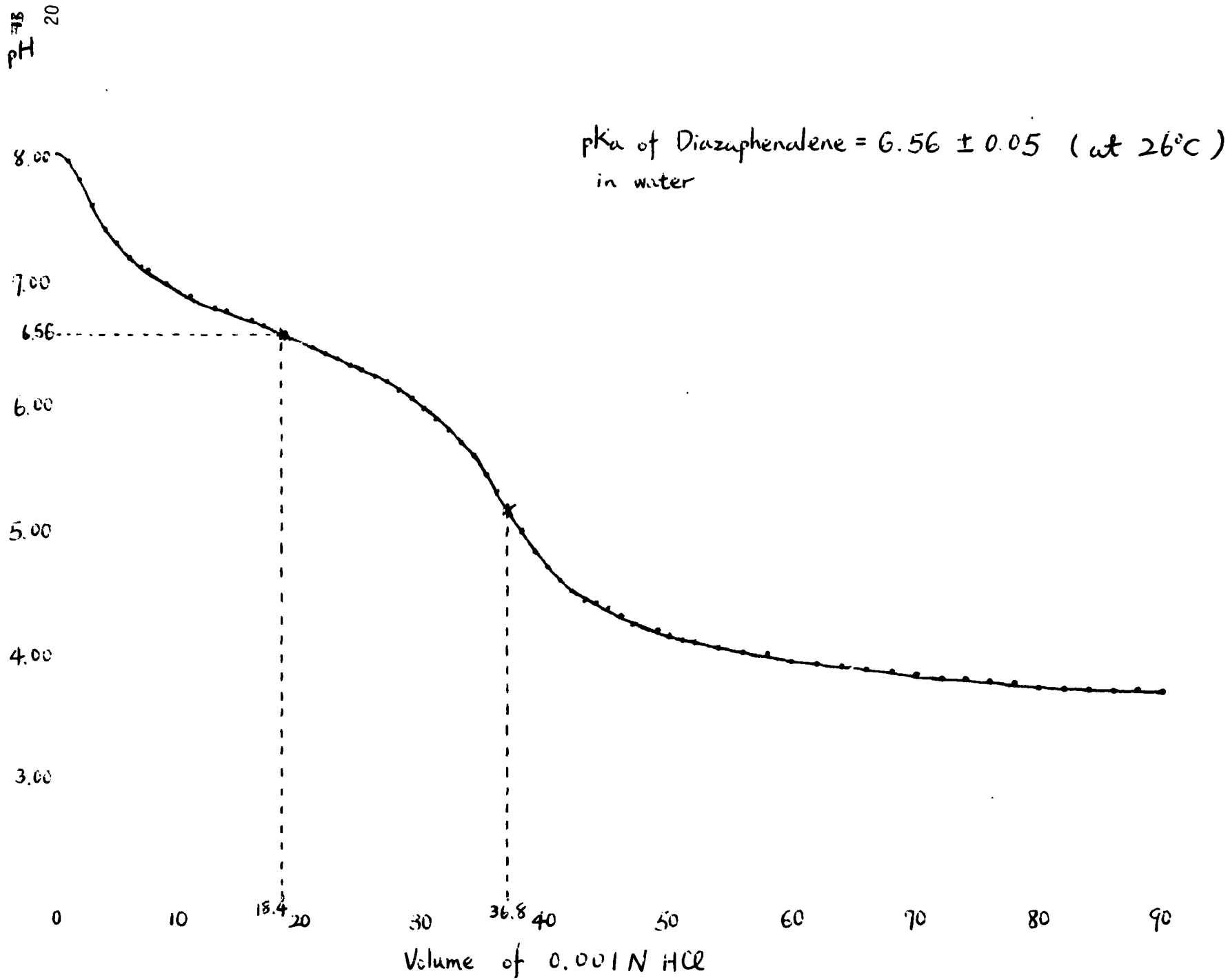
Further characterization of this mono-phenylazo compound and scale-up of this reaction need to be carried out.

Preparation of 7-Phenylazo-1,6-diazaphenalene 19. A solution of diazotized aniline was rapidly added to a solution of 1,6-diazaphenalene (0.84 g, 0.001 m) under the same conditions as described in the previous experiment. A dark red precipitate formed, and was filtered from the reaction medium and washed with water. The red monophenylazo compound 19 was separated from impurities by column chromatography: CI mass spectrum (NH_3) m/e (rel. intensity) 273 (M+1 for a monosubstitution product, 100), 245 (26), 171 (89); NMR ($CDCl_3$, 220 MHz). The NMR spectrum of this compound had two sets of AB doublets at 7.12 and 7.58 δ. This indicates a 7-phenylazo-1,6-diazaphenalene 19 has been formed. Further work on this reaction needs to be done to confirm the structure of 7-phenylazo-1,6-diazaphenalene 19.

Measurement of the pKa of 1,6-Diazaphenalene 1. The pKa value of 1,6-diazaphenalene 1 was determined by a potentiometric titration method. 100 ml of saturated 1,6-diazaphenalene 1 solution was titrated potentiometrically with 0.001 N HCl. On graph paper a plot of the titration curve was made; plot of pH on the ordinate against milliliters of titrant on the abscissa. To accurately determinate the end point volume, a plot of $\Delta pH/\Delta V$ vs. ml was carried out. One then locates the 50% neutralization point of the titration curve and from the pH at that point calculates the pKa of 1,6-diazaphenalene. The pKa of diazaphenalene in water is 6.56 ± 0.05 (at 26 ± 1°C).

Preparation of 2-Chloro-9-methoxy-1,6-diazaphenalene 2. To 2-oxo-2,3-dihydro-9-methoxy-1,6-diazaphenalene 24 (1.5 g, 0.007 m) was added 6 ml of phosphorus oxychloride. The mixture was then slowly warmed to 90°C and kept at that temperature for 1 hr. After cooling, the excess phosphorus oxychloride was removed under reduced pressure, and the residue was poured into ice water (50 ml). The red solution which resulted was basified with solid sodium carbonate at which time the product precipitated and was collected by filtration to provide a tan solid (1.4 g, 86%). This material was further purified by washing through a short column of alumina ($CHCl_3$) to give 1.1 g (68%) of an amorphous yellow solid 2: mp 231-235°C (dec.). IR (KBr) 1610 (s), 1540 (s), 1280 (s), 1250 (s); NMR (CF_3COOH) δ (s,3H), 6.4 (m,2H), 7.1-7.8 (m,3H); CI mass spectrum (NH_3) m/e 233 (M+1, 100) therefore M^+ = 232.

Attempted Reduction of 2-oxo-2,3-dihydro-9-methoxy-1,6-diazaphenalene 24 with Lithium Aluminum Hydride. 0.5 g (2.3 mmol) of the title compound in 40 ml THF was treated with a three-fold excess of lithium aluminum hydride and refluxed overnite. TLC indicated no reaction and an additional three equivalents of the hydride were added. After the mixture was held for an additional two days at reflux, TLC indicated only the presence of starting material 24 which was confirmed by an NMR spectrum of the crude reaction mixture and mixed melting point.


pKa of Diazaphenalene = 6.56 ± 0.05 (at 26°C)
in water
pH
8.00
7.00
6.56
6.00
5.00
4.00
3.00
0
10
18.4
20
30
36.8
40
50
60
70
80
90
Volume of 0.001 N HCl

The experiment was repeated with dioxane as solvent and again starting material was recovered after refluxing for three days. A five-fold excess of lithium aluminum hydride was employed in this experiment.

Attempted Nitration of 2-Oxo-2,3-dihydro-9-methoxy-1,6-diazaphenalene 24. To a solution of 24 (0.2 g, 1 mmol) in 2 ml sulfuric acid (at 0°C) was added with stirring potassium nitrate (0.1 g, 0.001 m) at 15 min periods. The solution was stirred overnight, poured into water (20 ml) and then basified (aqueous NH_3) to yield a black tar which was not characterized (baseline material on TLC).

Similarly, when a solution of the title compound (0.2 g) in acetic acid (5 ml) was treated with nitrous vapors (from As_2O_3 and HNO_3) for 2 min a black precipitate formed, which again defied characterization by TLC.

Preparation of 4-Methyl-5-amino-6-methoxy-8-phenylazoquinoline 25. Aniline (0.75 g, 0.008 m) was dissolved in hydrochloric acid (25 ml of 1 N) and was diazotized with sodium nitrite solution (7.5 ml of 1 N) with chilling. A mixture of 4-methyl-5-amino-6-methoxyquinoline 23 (1.5 g, 0.008 m) in acetic acid (15 ml, 1 N) was diluted to 150 ml, treated with 15 ml of saturated sodium acetate solution, chilled to about 10°C, and slowly treated with the diazo solution with stirring. The original red solution rapidly changed to deep purple and was stirred an additional 1/2 hr. The azo compound was precipitated by addition of aqueous ammonia, and subsequently extracted from the mother liquor with ethylacetate (2 x 100 ml). The combined extracts were dried (Na_2SO_4), and removal of the solvent was performed under reduced pressure to afford an oil. This oil crystallized from ether to provide red flakes (25, 1.6 g, 70% yield): mp 121-123°C; IR (KBr) 3300, 1620, 1565, 1450, 1340 and 1250 cm^{-1}; NMR ($CDCl_3$) δ 2.9 (s,3H), 3.9 (s,3H), 7.0-7.8 (m,7H), 8.6 (d,1H); mass spectrum at m/e 292 (M+, 100), 278 (40), 203 (26).

Attempted Carbonylation of 4-Methyl-5-amino-6-methoxy-8-phenylazoquinoline 25. To a solution of lithium diisopropylamide [7 mmol, 4 equivalents prepared by addition of diisopropylamine (0.7 g) in THF (5 ml) to n-butyllithium (5.8 ml of 1.2 m) cooled by a dry ice/$CHCl_3$ bath] was added dropwise to 4-methyl-5-amino-6-methoxy-8-phenylazoquinoline 25 (0.5 g, 1.7 mmol) in THF (20 ml). The resulting deep purple solution was stirred for 1/2 hr and poured onto a large excess of dry ice. After all the dry ice had evaporated, water (100 ml) was added and the THF was removed under reduced pressure. TLC indicated the presence of starting material as well as two new compounds whose structures are now being determined.

TLC alumina/ethylacetate R_f 0.71 (starting material);
0.50 (new compound);
0.07 (new compound).

The above experiment was originally carried out with two equivalents of LDA; however, only starting material was recovered from this attempt.

Attempted Preparation of 9-Methoxy-1,6-diazaphenalene 21 with Hydrazine over Pd/C. To a solution of 2-chloro-9-methoxy-1,6-diazaphenalene 2 (0.3 g, 0.0013 m) in ethanol (25 ml) was added palladium on carbon (0.1 g of 5%) and hydrazine (1 ml). The mixture was refluxed for three hrs, at which time, TLC indicated the absence of starting material 2 but showed the presence of two

new compounds. The solution was filtered, the solvent removed under reduced pressure and the residue which resulted was brought to pH = 9 with aqueous ammonia. The basic solution was extracted with ethylacetate and the organic layer dried (Na_2SO_4). The solvent was removed under reduced pressure to provide an oil which was chromatographed on silica gel (eluent - ethylacetate).

The compound of highest R_f was unstable and appeared to be the 2-hydrazine derivative by NMR spectroscopy. The compound of lower R_f decomposed during the chromatography.

This reaction will be repeated until it works!

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